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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,421	09/08/2008	David Ray Filpula	213.1204-PCT-US	5480

20311 7590 03/24/2010

LUCAS & MERCANTI, LLP
475 PARK AVENUE SOUTH
15TH FLOOR
NEW YORK, NY 10016

EXAMINER	
HISSONG, BRUCE D	

ART UNIT	PAPER NUMBER
1646	

NOTIFICATION DATE	DELIVERY MODE
03/24/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

info@lmiplaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/590,421	FILPULA ET AL.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-109* is/are pending in the application.

4a) Of the above claim(s) *72,73 and 99-109* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55-71 and 74-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *8/22/2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/22/2006, 8/11/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *10590421_SEQ_COMP*.

DETAILED ACTION

Election/Restrictions

1. Applicant's election on 11/23/2009, with traverse, of Group I, claims 55-98 and the structure depicted on page 14 of Applicants' 11/23/09 response, and the species election of sodium acetate, mannitol, polyethylene glycol, an activated polyethylene glycol having the structure $mPEG_2CH_2CH_2CH_2CHO$, and the terminal reactive moiety depicted on page 16 of the 11/23/09 response, is acknowledged.

The traversal is on the ground(s) that the products of Group I are necessarily used by the methods of Groups II and III, and therefore there would be no burden to search and consider Groups I, II, and III at the same time. The Applicants also argue that the technical feature of the invention is described in claims 55-98, and because the methods of Groups II and III utilize the product of Group I, the Groups I, II, and III relate to a single inventive concept under PCT Rule 13.1 by sharing the same or corresponding special technical features. The Applicants further assert that such of search of Groups II and III will overlap with a search of Group I.

This is not found persuasive because, as set forth in the requirement for restriction mailed on 10/21/2009, the claims fail to share a special technical feature with the other claims, wherein the special technical feature, as defined by PCT rules, is a feature that makes a contribution over the art. As set forth on pages 2-3 of the 10/21/09 requirement for restriction, claim 1 lacks such a feature because Drustrup (US 20030138403) discloses the features of claim 1, and therefore restriction among the different inventions is proper. Regarding Applicants' arguments that there would be no undue burden to search all of Groups I, II, and III, it is noted that the method of Group III, as currently written, reads preparation of conjugates other than interferon (IFN)-comprising conjugates, and therefore potentially encompasses subject matter outside of what is elected in Group I. Similarly, Group II is drawn to methods of administering IFN conjugates to patients in need of such administration, which could potentially encompass patients with any disease, disorder, or condition, as no specific disease(s) is recited in the claims. A search of the subject matter of Group I could potentially uncover art relevant to the product, but due to the unduly broad language of the claims of Group II, may not uncover art for all possible diseases, disorders, or conditions.

The requirement is still deemed proper and is therefore made FINAL.

2. In the response received on 11/23/2009, the Applicants cancelled claims 1-54 and added new claims 55-109. Claims 55-98 read on the elected subject matter of Group I.

3. Therefore, claims 55-109 are pending, with claims 99-109 withdrawn as non-elected subject matter. Furthermore, with the election of the branched polymer depicted on page 14 of the 11/23/09 response, claims 72-73, drawn to linear polymers, as also withdrawn as non-elected subject matter.

4. Claims 55-71 and 74-98 are the subject of this office action.

Information Disclosure Statement

1. The IDS received on 12/22/2006 has been considered. Citations A36 and A38 were lined-through as being duplicate submissions of citations A21 and A1, respectively. Citations A12, A19, A20, and A49 were lined-through for lacking a complete citation. Specifically, citations A12, A19, and A20 omitted the publication date, while citation A49 omitted the appropriate page numbers. Complete citations for A12, A19, A20, and A49 appear on the accompanying PTO-892 form.

2. The IDS received on 8/11/2009 has been considered. Citation 1 (20030138403, Drustrup) was lined-through because it was previously submitted in the 12/22/06 IDS (as citationA6), and citation 7 as lined-through as it was previously submitted in the 12/22/06 IDS (as citationA49).

Claim Objections

1. Claims 74, 76, and 97 are objected to for recitation of non-elected subject matter. Specifically, with the election of the branched polymer structure depicted on page 14 of the 11/23/2009 response, the recitation of other branched polymers represents a recitation of non-elected subject matter.

2. Claim 59 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Specifically, claim 59 recites a pH range (from about 2.5 to about 8.5) that falls outside the recited range in the parent claim 55, which sets pH 3 as the lower limit.

3. Claims 68-69 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Specifically, claims 68-69 depend from claim 67, and recite excipients selected from the group consisting of sucrose, trehalose, mannitol and glycerol *or a combination thereof* (claim 68), and mannitol and sucrose *or a combination thereof* (claim 69). However, claim 67 recites "the excipient selected from the group consisting of glucose, ribose,……..mannitol, and xylitol", and as written can only have 1 excipient while dependent claims 68-69, by reciting "or a combination thereof" can have more than one excipient. It is suggested that this objection may be overcome by amending claim 67 to recite "or a combination thereof" similar to claims 68-69.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 55-71, 80-84, and 86-95 are rejected under 35 U.S.C. 102(e) as being anticipated by Drustrup (US 20030138403 – cited in the IDS received on 12/22/06).

The claims of the present invention are drawn to a composition comprising an interferon conjugated to a polyalkylene oxide polymer having a molecular weight of at least about 12 kDa, and optionally, an excipient and a buffer, wherein the pH range of the solution is from about 3 to about 11. The claims further recite the claimed composition comprising IFN-β-1b, a surfactant, such as selected from poloxyethylene sorbitol esters and polyethylene glycol, pH ranges from about 2.5 to about 8.5, and from about 3 to about 5. The claims also recite the IFN composition comprising a buffer, including sodium acetate, wherein the ionic strength is about 10 mM and the buffer is in a concentration of about 3-10 mM, and wherein the composition also comprises monosaccharides, disaccharides, and alditols, and specifically mannitol. Also recited is polyalkylene oxide polymer ranges from about 12 kDa to about 60 kDa, and more specifically, 30 kDa and 40 kDa, and wherein the polyalkylene oxide polymer is

conjugated to IFN-β via the alpha-amino terminal of IFN-β, or via an epsilon group of a lysine residue. The claims also recite a biologically-active polymer-IFN conjugate wherein at least about 65 percent of the antiviral activity is retained relative to native IFN-β-1b, using the EMC/Vero or EMC/A549 antiviral assay, and wherein at least about 20 percent of the antiviral activity is retained. The claims also recite method of preparing the biologically active polymer-IFN conjugate.

Drustrup teaches a formulation comprising IFN-β conjugated to polyethylene glycol having a molecular weight of 12 kDa, wherein said formulation also comprises an acetate buffer at 10 mM, and mannitol (an excipient), wherein the pH of said formulation is 5.5 (see Example 5), thus meeting the limitations of claims 55, 59-60, 62-69, and 71. Furthermore, Drustrup teaches that the IFN of the formulation can be IFN-α, IFN-β, or a variant thereof (paragraph 0022), and therefore encompassing IFN-β-1b, which could be considered as a variant of IFN-β and meeting the limitations of claim 56, formulations comprising IFN at 0.1 to 10 mg/ml (paragraph 0253), and teaches pH ranges from 3.0 to 8.0, meeting the limitations of claims 59-61 and 83-84. Drustrup also teaches incorporation of polyethylene glycol into the formulations (paragraph 0243), meeting the limitations of claims 57-58 and 70. Drustrup also teaches various methods of conjugation/attachment of PEG to IFN-β polypeptides, including conjugation to the amino-terminus of IFN, and conjugation to lysine residues (see paragraph 0040, 0386, see also the table between paragraphs 0037 and 0038, which describes attachment of various activated PEG molecules to various regions/residues), meeting the limitations of claims 81-82, and because conjugation to lysine would inherently involve an amine linkage via the amino group of lysine, claim 80 is also anticipated. Furthermore, Drustrup discloses specific methods of preparing conjugates comprising IFN and PEG (see Examples 3 and 5, paragraph 0384-0386), meeting the limitations of claim 88-95.

Finally, regarding the limitations that the claimed conjugate retain at least about 65 percent, or at least about 20 percent of the antiviral activity relative to native IFN-β-1b using the EMC/Vero or EMC/A549 antiviral assays, it is noted that while Drustrup does not specifically teach these limitations, the formulations and methods of conjugation disclosed by Drustrup are the same as those presently claimed, and in absence of evidence to the contrary, the formulations produced by the methods of conjugation of Drustrup would be expected to exhibit these activities. Because the USPTO does not have the facilities for testing the conjugates/formulations of Drustrup, the burden is on the Applicants to show a novel and unobvious difference between the claimed compositions/conjugates and those of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claim 85 is rejected under 35 U.S.C. 103(a) as being unpatentable over Drustrup (US 20030138403). Claim 85 is drawn to the composition of claim 55, wherein the IFN conjugate is present at a concentration of about 0.05 mg/ml to about 3 mg/ml, and 1-5% mannitol, and 3-10 mM acetic acid, wherein the pH is about 3.7

The disclosure of Drustrup is discussed above. Although Drustrup teaches IFN-b-1b formulations comprising IFN-β conjugated to PEG at 12 kDa, mannitol, and acetate buffer, and at various pH ranges, Drustrup does not specifically teach a formulation comprising IFN-β-1b conjugated to a polyalkylene oxide polymer having a weight of at least 12 kDa and further comprising the exact ranges of mannitol and acetic acid concentrations, wherein the pH is about 3.7. However, because Drustrup teaches the essential elements of the composition, namely IFN-β-1b conjugated to 12 kDa PEG, and wherein the composition further comprises mannitol and acetic acid/acetate buffer, and various pH ranges are disclosed which encompass the claimed pH, it would have been obvious to one of ordinary skill in the art to optimize the concentrations of IFN-β, manntiol, and acetic acid/acetate, as well as the pH, in order to create the most biologically active composition. MPEP 2144.05 states:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 454, 105 USPQ 223, 235, (CCPA 1955).

In the instant case, the general conditions of the claim are disclosed in Drustrup, as set forth above, and thus it would not be inventive to optimize these variables by routine experimentation.

2. Claims 74, 76-79, and 96-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Drustrup (US 20030138403) in view of McManus *et al* ("McManus" - US 20070166277).

Claims 74, 76-69, and 96-98 are drawn to the claimed composition comprising IFN conjugated to a polyalkylene oxide of at least 12 kDa, wherein the polyalkylene oxide polymer is the elected polymer depicted on page 14 of the Applicants' response of 11/23/2009, wherein the molecular weight of the

polyalkylene oxide polymer ranges from about 12 kDa to about 60 kDa, and specifically 30 kDa or 40 kDa. The claims also recite a conjugate comprising an activated polyethylene glycol with an $mPEG_2CH_2CH_2CH_2CHO$ structure, and methods of preparing an IFN conjugate comprising the elected polyalkylene oxide shown on page 14 of the 11/23/09 response, and wherein the activated polyethylene glycol comprises the elected terminal reactive moiety shown on page 16 of the 11/23/09 response.

The disclosure of Drustrup is discussed above. Drustrup is silent regarding conjugation of IFN-β to the polyalkylene oxide polymer shown on page 14 of the 11/23/09 response, or comprising the terminal reactive moiety shown on page 16 of the same response. However, McManus teaches a 40 kDa succimidyl ester of PEG_2 which is identical to the elected polyalkylene oxide polymer shown on page 14 of the 11/23/09 response, wherein this polymer also comprises the elected terminal reactive moiety, and has the overall structure shown on page 16 of the 11/23/09 response (see Example 6 of McManus). McManus teaches the use of this succimidyl PEG2 ester for the use of conjugating PEG to various polypeptides, including IFN-β (see Example 15). McManus also teaches polymeric agents with a $CH_2CH_2CH_2CHO$ spacer structure separating the polymer, such as PEG, and the biological protein (paragraph 0172).

Therefore, it would have been obvious to one of ordinary skill in the art, at the time the present invention was conceived, to prepare a conjugate comprising IFN-b conjugated to a polyalkylene oxide polymer of at least 12 kDa, wherein the polyalkylene oxide polymer is the polymer elected by Applicants and shown on page 14 of the 11/23/09 response, and wherein this polymer also comprises the terminal reactive moiety shown on page 16 of the 11/23/09 response. The motivation to do so comes from the disclosure of Drustrup, which teaches compositions comprising IFN-β wherein the IFN-β is conjugated to a polyalkylene oxide polymer (PEG) that is 12 kDa (Example 5), and also teaches conjugation to PEG molecules having a molecular weight between 10 kDa and 40 kDa (paragraph 0070). Further motivation comes from McManus, which discloses a polyalkylene oxide moiety with the same structure as the elected polyalkylene oxide shown on page 14 of the 11/23/09, and also comprising the terminal reactive moiety shown on page 16 of the 11/23/09 response, and conjugation of this polyalkylene oxide moiety to polypeptides such as IFN-β. Therefore, because Drustrup teaches conjugation of IFN-β to polyalkylene oxide polymers having a molecular weight of at least 12 kDa, and McManus teaches a specific polyalkylene oxide polymer that is identical to Applicants' elected polymer, and the use of this polymer for conjugation to polypeptides such as IFN-β, it would have been obvious to one of ordinary skill in the art to conjugate the succimidyl PEG ester of McManus to IFN-β and create a composition comprising acetate buffer, mannitol, PEG as a stabilizer/surfactant, and at the pH ranges taught by Drustrup.

3. Claim 75 is rejected under 35 U.S.C. 103(a) as being unpatentable over Drustrup (US 20030138403) in view of Saifer *et al* ("Saifer" - US 20040126361 – cited in the IDS received on 12/22/2006).

Claim 75 is drawn to the composition of claim 56, wherein the IFN-β-1b comprises the amino acid sequence of SEQ ID NO: 1. The disclosure of Drustrup is discussed above. Although Drustrup clearly contemplates formulations comprising an IFN conjugated to PEG, wherein the IFN is IFN-α, IFN-β, or variants thereof (paragraph 0022), of which IFN-β-1b would be an art-recognized variant of IFN-β, Drustrup does not explicitly teach an IFN polypeptide comprising the sequence of SEQ ID NO: 1.

However, Saifer teaches an IFN-β-1b polypeptide which is identical to the amino acid sequence of SEQ ID NO: 1 (see accompanying sequence comparison). Saifer also teaches conjugation of this polypeptide to PEG (see Example 4), and teaches that pharmaceutical compositions comprising IFN-β are useful for treating IFN-β-responsive disorders, including certain cancers, infectious disease, autoimmune disorders (see claims 25, 50, 55-58).

Therefore, one of ordinary skill in the art, at the time the present invention was conceived, would have been motivated to create a formulation comprising the IFN-β polypeptide of SEQ ID NO: 1, wherein this IFN-β polypeptide was conjugated to a polyalkylene oxide polymer of at least 12 kDa, and wherein said formulation also comprised an excipient and a buffer, wherein the pH range of the solution is from about 3 to about 11. The motivation to do so comes from the combined teachings of Drustrup and Saifer, which collectively teach a therapeutically useful IFN-β which is identical to SEQ ID NO: 1 of the instant application and which can be conjugated to PEG (Saifer), and a formulation for such IFN-β polypeptides comprising an excipient, a buffer, and wherein the pH range of the solution is from about 3 to about 11 (Drustrup). Thus, one of ordinary skill in the art, knowing that the formuation of Drustrup is an effective formulation for therapeutic IFN-β polypeptides, would be motivation to formulate the IFN-β-1b of Saifer b the methods of Drustrup to create an effective therapeutic formulation of IFN-β-1b useful for treatment of IFN-β-responsive disorders.

Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D. whose telephone number is (571)272-3324. The examiner can normally be reached on 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D. can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Bruce D. Hissong
Art Unit 1646

/Robert Landsman/
Primary Examiner, Art Unit 1647